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Prevention of the Acute Conditioned Necrosis Phenomenon

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Zusammenfassung. Versuche an Ratten bestätigen und erweitern die Beobachtung, daß Behandlung mit zahlreichen Mastzellentladern, Serotonin oder Histamin den Organismus für die Erzeugung akuter lokaler Nekrosen sensibilisiert, die dann an jenen Stellen auftreten, wo gleichzeitig bestimmte Gewebsreizstoffe (z. B. hypertonische NaCl-Lösung) in das Bindegewebe eingeführt werden. Diese akute, konditionierte Nekrose (ACN) kann durch Vorbehandlung mit Mastzellentladern oder Histamin verhindert werden, während Serotonin — zumindest unter unseren Versuchsbedingungen — keine solche Schutzwirkung erkennen ließ. Vorbehandlung mit Antihistamin- und Antiserotoninpräparaten (Cyproheptadin und Phenoxybenzamin) verhindert ebenfalls die Entwicklung der ACN, aber die Schutzwirkung aller testierten Prophylaktica ist von kurzer Dauer; sie unterscheidet sich dadurch von der anhaltenden Immunität, welche durch serologische Reaktionen herbeigeführt wird.

Summary. Experiments on the rat confirm and extend the observation that conjoint treatment with numerous mast-cell dischargers, 5-HT or histamine sensitizes the organism for the production of acute necrosis at sites where certain tissue irritants, such as hypertonic NaCl, are introduced into the connective tissue. Thic acute conditioned necrosis (ACN) can be prevented by pretreatment with mast-cell dischargers or histamine while — at least under the conditions of these experiments — 5-HT exhibited no such protective effect. Pretreatment with antihistaminic and antiserotonin compounds (cyproheptadine and phenoxybenzamine) likewise prevents the development of the ACN but the protective action of all prophylactic agents tested is of short duration thereby differing from the long lasting immunity induced by specific serologic reactions.

It has been observed recently that after sensitization by systemic treatment with certain "conditioning factors" (e.g., mast-cell dischargers, histamine, serotonin), extensive skin necrosis is produced by the subcutaneous administration of normally well-tolerated doses of certain "challengers" (e. g., hypertonic solution, bile, proteolytic enzymes, acetic acid) (SELYE, 1966; SELYE, ROHAN, and PAHK, in press). This phenomenon of "acute conditioned necrosis" (ACN) occurs a few hours after challenge; thereby it differs from the "delayed conditioned necrosis" (DNC) which develops much more slowly — for example after conditioning with glucocorticoids — at sites of treatment with long-acting inflammatory irritants (SELYE, 1953, 1954).

In the present communication we should like to report upon observations showing that tissues can be protected against this acute necrosis by pretreatment with mast-cell dischargers, cyproheptadine and phenoxybenzamine.

Methods

910 female Sprague-Dawley rats with a mean body weight of 100 g (range 90—110 g) were subdivided into 91 equal groups and treated as outlined in Tab. 1.

As conditioning or protective factors we used the following:

Cyproheptadine: Periactin®, 1-methyl-4-(5-dibenzo-[a-e]-cycloheptatrienylidene)-piperidine HCl (Merck, Sharp & Dohme, West Point, Pa., U.S.A.).

Dextran: M. W. 75,000, a 6% solution stabilized by 5.7% sorbitol N. F. (Abbott Laboratories, North Chicago, U.S.A.).

Dextrin: British gum or starch gum, a polysaccharide [$(C_6H_{10}O_5)$ n X H_2O] prepared by incomplete hydrolysis of starch (Difco Labs., Detroit, U.S.A.).

Histamine: Histamine phosphate (Abbott).

5-HT: 5-hydroxytryptamine, Serotonin creatinine sulfate (Nutritional Biochemicals, Cleveland, Ohio, U.S.A.).

Phenoxybenzamine: Dibenzyline®, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-benzylamine HCl (Smith Kline & French, Montreal, Canada).

Polymyxin: Polymyxin-B sulfate (Abbott).

Reserpine: (CIBA Co., Montreal, Canada).

Restraint: Achieved by immobilizing the animals on a board for 24 hours beginning 5 hours before challenge, according to our standard technique (SELYE, 1958).

Spinal cord transection: Performed with a thermocautery, above the seventh cervical vertebra just before challenge.

The only *challenger* used in this series was sodium chloride.

Unless otherwise stated, all conditioning agents were injected intravenously (into the jugular vein under light ether anesthesia) in 1 ml or subcutaneously (on the belly) in 0.2 ml of distilled water. The challenging hypertonic NaCl solution was administered into the deep connective tissue, on the middle of the back, at the dose of 400 mg in 2 ml of distilled water. Great care was taken to avoid the injection of this concentrated solution into the dermis since, in this case, necrosis ensues even without any conditioning treatment. Whenever any of these agents was given to sensitize to the necrotizing action of hypertonic NaCl, it was applied just before the latter while in the experiments designed to show a protection, pretreatment with some of the same agent was given before the evocative treatment, at the times specified in the text.

In the absence of effective prophylaxis, the necroses became evident at the challenged sites, as more or less circular cyanotic edematous plaques, usually within 30 to 60 min. However, in order to permit perfect delimitation of the affected areas, the animals were allowed to survive about 24 hours at which time the maximal and minimal diameters of the necrotic plaques were determined, the means of these two measurements being registered in the Tables, with their standard errors.

Histologic studies using the PAS and multipurpose polychrome techniques (SELYE, 1965) showed that the lesions occurring at the sites of challenge consisted essentially of bland necroses involving all layers of the skin and part of the subcutis. In the surrounding tissue there were also edema, intense mast-cell degranulation, and thrombosis of veins and venules. Since these changes were essentially the same in all groups, they need not be further discussed here.

Results

We have summarized our results in six Tables, which are almost self-explanatory. Our first problem was the *prevention of the ACN by pretreatment with various drugs*. In Part I of the relevant work (Tab. 1), we employed very high doses of dextrin, 5-HT or histamine as conditioners and

Table 1. *Prevention of ACN by pretreatment with various drugs (Part 1)*

Group	Pretreatment	Conditioner*	Necrosis (mm)
1	None	Dextrin 250 mg i.v.	30 ± 1.2
2	Dextran 60 mg i.v.	Dextrin 250 mg i.v.	0
3	Dextrin 250 mg i.v.	Dextrin 250 mg i.v.	2 ± 1.6
4	5-HT 2 mg s.c.	Dextrin 250 mg i.v.	31 ± 1.0
5	Histamine 40 mg s.c.	Dextrin 250 mg i.v.	32 ± 3.1
6	Cyproheptadine 0.5 mg i.v.	Dextrin 250 mg i.v.	11 ± 4.8
7	Phenoxybenzamine 1 mg s.c.	Dextrin 250 mg i.v.	4 ± 1.6
8	None	5-HT 2 mg s.c.	32 ± 1.6
9	Dextran 60 mg i.v.	5-HT 2 mg s.c.	30 ± 1.6
10	Dextrin 250 mg i.v.	5-HT 2 mg s.c.	33 ± 1.3
11	5-HT 2 mg s.c.	5-HT 2 mg s.c.	34 ± 0.8
12	Histamine 40 mg s.c.	5-HT 2 mg s.c.	34 ± 1.2
13	Cyproheptadine 0.5 mg i.v.	5-HT 2 mg s.c.	25 ± 2.8
14	Phenoxybenzamine 1 mg s.c.	5-HT 2 mg s.c.	11 ± 2.8
15	None	Histamine 40 mg s.c.	20 ± 2.8
16	Dextran 60 mg i.v.	Histamine 40 mg s.c.	11 ± 3.4
17	Dextrin 250 mg i.v.	Histamine 40 mg s.c.	12 ± 4.5
18	5-HT 2 mg s.c.	Histamine 40 mg s.c.	16 ± 3.3
19	Histamine 40 mg s.c.	Histamine 40 mg s.c.	7 ± 3.1
20	Cyproheptadine 0.5 mg i.v.	Histamine 40 mg s.c.	5 ± 3.0
21	Phenoxybenzamine 1 mg s.c.	Histamine 40 mg s.c.	11 ± 3.7

* The conditioner was invariably administered 5 hours after the pretreatment and followed immediately by challenge with 200 mg of NaCl in 2 ml of distilled water injected under the shaved skin of the back.

accordingly obtained extensive necroses at the sites of challenge in the unpretreated control animals (Groups 1, 8 and 15). In the other groups, pretreatment was arbitrarily administered 5 hrs prior to conditioning + challenge. Under these circumstances the dextrin-conditioned necrosis was abolished or at least significantly inhibited by pretreatment with dextran, dextrin, cyprophetadine and phenoxybenzamine (Groups 2, 3, 6, 7), while 5-HT and histamine pretreatment offered no protection (Groups 4, 5).

The ACN produced by 5-HT + NaCl was significantly diminished only by phenoxybenzamine (Group 14), while dextran, dextrin, 5-HT, histamine and cyproheptadine were ineffective in this respect (Groups 9—13).

The necrosis induced by histamine + NaCl was less extensive than that seen after conditioning with dextrin or 5-HT (compare Group 15 with Groups 1 and 8) and hence its partial inhibition by dextran, dextrin, histamine, cyproheptadine and phenoxybenzamine (Groups 16, 17, 19, 20, 21) is less conclusive, but evidently 5-HT again failed to offer a statistically significant protection (Group 18).

The most striking outcome of this first experiment was the demonstration that when the mast-cell discharger dextrin is used as a conditioner, pretreatment with mast-cell dischargers, cyproheptadine or phenoxybenzamine offers a great deal of protection. This was not the case when 5-HT was used as a conditioner; against the latter only phenoxybenzamine exhibited some degree of prophylactic potency.

A second experiment was performed therefore using smaller doses of dextrin and 5-HT for conditioning, but retaining the original comparatively high dosage of the various agents for pretreatment. In this manner we hoped to show whether a better prophylaxis is obtained when the dose of the potentially protective agent is considerably higher than of the pathogen. Tab. 2 indicates that, under these circumstances, the conditioning effect of dextrin (Groups 1—7) was totally abolished by pretreatment with dextran or dextrin, less markedly by cyproheptadine, phenoxybenzamine and histamine, but uninfluenced (in fact perhaps aggravated) by pretreatment with 5-HT. In sharp contrast to these findings, the conditioning effect of 5-HT (Groups 8—14) could not be inhibited by any of the agents tested and indeed appeared to be aggravated by some of them.

The first two experimental series suggested the existence of some *proportionality between the effective prophylactic and conditioning doses* of the agents used. This point was further investigated in the third series of our investigations (Tab. 3). Again, pretreatment was always administered 5 hours before the conjoint administration of the conditioning and challenging agent. Dextrin was employed throughout for pretreatment and conditioning. For the latter purpose, 25 mg were employed in Groups 1—6 and 25 times this amount in Groups 7—12. For pretreatment the lowest dose of dextrin used was 1 mg, this amount being raised 5 times in each successive group.

It is clear that pretreatment with 25 mg of dextrin is just sufficient to induce an almost complete suppression of the ACN elicited by conditioning with the same amount (Group 4); the effect of conditioning with 625 mg was less completely suppressed by the prophylactic administra-

Table 2. *Prevention of ACN by pretreatment with various drugs (Part 2)*

Group	Pretreatment	Conditioner*	Necrosis (mm)
1	None	Dextrin 25 mg i.v.	20 ± 3.9
2	Dextran 60 mg i.v.	Dextrin 25 mg i.v.	0
3	Dextrin 250 mg i.v.	Dextrin 25 mg i.v.	0
4	5-HT 2 mg s.c.	Dextrin 25 mg i.v.	30 ± 3.1
5	Histamine 40 mg s.c.	Dextrin 25 mg i.v.	12 ± 3.1
6	Cyproheptadine 0.5 mg i.v.	Dextrin 25 mg i.v.	7 ± 2.9
7	Phenoxybenzamine 1 mg s.c.	Dextrin 25 mg i.v.	9 ± 2.7
8	None	5-HT 1 mg s.c.	16 ± 3.0
9	Dextran 60 mg i.v.	5-HT 1 mg s.c.	22 ± 1.9
10	Dextrin 250 mg i.v.	5-HT 1 mg s.c.	24 ± 3.3
11	5-HT 2 mg s.c.	5-HT 1 mg s.c.	27 ± 3.1
12	Histamine 40 mg s.c.	5-HT 1 mg s.c.	22 ± 2.1
13	Cyproheptadine 0.5 mg i.v.	5-HT 1 mg s.c.	21 ± 1.1
14	Phenoxybenzamine 1 mg s.c.	5-HT 1 mg s.c.	12 ± 2.8

* The conditioner was invariably administered 5 hours after the pretreatment and followed immediately by challenge with 200 mg of NaCl in 2 ml of distilled water injected under the shaved skin of the back.

Table 3. *Proportionality between prophylactic and conditioning dose of dextrin*

Group	Pretreatment	Conditioner*	Necrosis (mm)
1	None	Dextrin 25 mg i.v.	27 ± 3.8
2	Dextrin 1 mg i.v.	Dextrin 25 mg i.v.	25 ± 0.5
3	Dextrin 5 mg i.v.	Dextrin 25 mg i.v.	26 ± 3.2
4	Dextrin 25 mg i.v.	Dextrin 25 mg i.v.	4 ± 3.6
5	Dextrin 125 mg i.v.	Dextrin 25 mg i.v.	0
6	Dextrin 625 mg i.v.	Dextrin 25 mg i.v.	0
7	None	Dextrin 625 mg i.v.	27 ± 1.1
8	Dextrin 1 mg i.v.	Dextrin 625 mg i.v.	29 ± 1.8
9	Dextrin 5 mg i.v.	Dextrin 625 mg i.v.	31 ± 1.7
10	Dextrin 25 mg i.v.	Dextrin 625 mg i.v.	16 ± 2.6
11	Dextrin 125 mg i.v.	Dextrin 625 mg i.v.	0
12	Dextrin 625 mg i.v.	Dextrin 625 mg i.v.	0

* The conditioner was invariably administered 5 hours after the pretreatment and followed immediately by challenge with 200 mg of NaCl in 2 ml of distilled water injected under the shaved skin of the back.

tion of 25 mg (Group 10) but the difference was not significant. Thus there is little, if any, proportionality between the doses of dextrin required for protection against small or large amounts of the same substance. Certainly this difference, if real, is not very striking since pretreatment with 125 mg is fully effective against conditioning with either 25 mg or 625 mg of the same mast-cell discharger.

Table 4. *Time required to induce protection against dextran*

Group	Pretreatment	Time interval* (hours)	Necrosis (mm)
1	None (not conditioned controls)	0	0
2	None (conditioned controls)	0	30 ± 0.9
3	Polymyxin 2 mg s.c.	0	35 ± 1.0
4	Polymyxin 2 mg s.c.	1/2	26 ± 2.7
5	Polymyxin 2 mg s.c.	5	0
6	Dextran 60 mg i.v.	0	30 ± 1.4
7	Dextran 60 mg i.v.	1/2	0
8	Dextran 60 mg i.v.	5	0
9	Dextrin 250 mg i.v.	0	32 ± 1.0
10	Dextrin 250 mg i.v.	1/2	0
11	Dextrin 250 mg i.v.	5	0
12	5-HT 2 mg s.c.	0	37 ± 1.3
13	5-HT 2 mg s.c.	1/2	29 ± 2.0
14	5-HT 2 mg s.c.	5	20 ± 3.6
15	Histamine 40 mg s.c.	0	30 ± 1.3
16	Histamine 40 mg s.c.	1/2	5 ± 2.4
17	Histamine 40 mg s.c.	5	0
18	Cyproheptadine 0.5 mg i.v.	0	0
19	Cyproheptadine 0.5 mg i.v.	1/2	0
20	Cyproheptadine 0.5 mg i.v.	5	0
21	Phenoxybenzamine 1 mg s.c.	0	24 ± 3.5
22	Phenoxybenzamine 1 mg s.c.	1/2	0
23	Phenoxybenzamine 1 mg s.c.	5	0
24	Reserpine 0.05 mg s.c.	0	29 ± 3.4
25	Reserpine 0.05 mg s.c.	1/2	21 ± 4.0
26	Reserpine 0.05 mg s.c.	5	10 ± 3.1
27	Spinal cord transection	0	28 ± 1.2
28	Spinal cord transection	1/2	33 ± 1.8
29	Spinal cord transection	5	28 ± 1.3
30	Restraint	5	22 ± 2.0

* As a conditioner, 60 mg of dextran was administered intravenously to all animals except the not conditioned controls (Group 1) simultaneously with challenge by 200 mg of NaCl in 2 ml of distilled water injected under the shaved skin of the back. The figures in this column refer to the time intervals elapsing between pretreatment and the conjoint administration of conditioner + challenger (Groups 2—29). Restraint (Group 30) was started 5 hours before administration of dextran + NaCl and continued for 19 hours thereafter.

In the preceding experiments we arbitrarily selected a time interval of 5 hours between pretreatment and conditioning. It remained to be seen whether concurrent treatment with two potential conditioners, or pretreatment with one shortly before the other would be equally effective. Therefore, an additional series of experiments was performed to determine *the time required to induce protection* against the ACN. Here, 60 mg of dextran was used throughout as a conditioner but a variety of agents were employed for pretreatment. Some of these were already known to have conditioning potency (polymyxin, dextran, dextrin, 5-HT and histamine); others were selected because of their blocking effect upon such mast-cell products as histamine and serotonin (cyproheptadine, phenoxybenzamine), their catecholamine discharging effect (reserpine) or their general stressor action (spinal cord transection, forced restraint).

It will be noted from Tab. 4 that, as expected, challenge without conditioning produces no necrosis even without any prophylactic pretreatment (Group 1) while conditioning + the same challenge elicits pronounced response (Group 2). At the dose levels used here, polymyxin (Groups 3—5) dextran (Groups 6—8), dextrin (Groups 9—11), histamine (Groups 15—17), cyproheptadine (Groups 18—20), and phenoxybenzamine (Groups 21—23) all offered perfect protection when given 5 hours before conditioning and some were effective even when administered only 30 min before the latter. On the other hand, none of these agents, except cyproheptadine, induced any protection when given concurrently with the conditioning + challenge (Fig. 1). It was again confirmed that 5-HT offers no protection against the ACN under these circumstances (Groups 12—14). The previously untested reserpine (Groups 24—26) as well as the two stressors, spinal cord transection (Groups 27—29) and restraint (Group 30), were likewise inefficacious. It is evident therefore that the phenomenon of protection against the ACN is largely specific.

Having established that, in most instances, pretreatment 5 hours before conditioning + challenge can prevent the ACN, *the duration of the protection* was examined using polymyxin as an example both for pretreatment and for conditioning. In all instances 1 mg of polymyxin was given subcutaneously as a conditioner, this being immediately followed by the usual subcutaneous challenge with hypertonic saline (Tab. 5).

In itself this treatment produces an extensive cutaneous necrosis (Group 1) but this response is totally inhibited by pretreatment with 2 mg of polymyxin given anywhere between 7 and 3 hours prior to conditioning + challenge (Groups 4—8). Even when polymyxin is injected 2 hours before conditioning + challenge some protection can be noted (Group 9) but the effect of pretreatment 24 or 17 hours before (Groups 2 and 3) apparently vanished too early to be of prophylactic value. Conversely, treatment with this large amount of polymyxin 1 hour before condition-

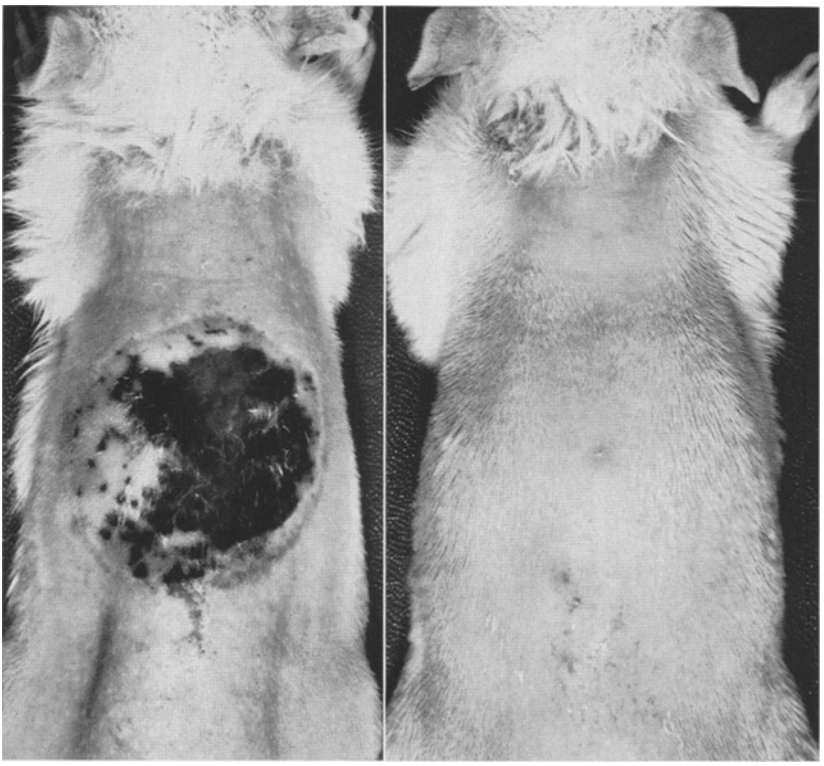

Fig. 1. *Typical appearance of the ACN and its prevention by cyproheptadine.* — *Left:* Large roughly circular necrotic patch on the back of a rat conditioned by 60 mg of dextran i.v. and simultaneously challenged with hypertonic NaCl. *Right:* Similarly treated rat in which the development of the lesion was prevented by pretreatment with cyproheptadine

Table 5. *Duration of protection by polymyxin against polymyxin*

Group	Pretreatment	Time interval* (hours)	Necrosis (mm)
1	None	—	25 ± 2.4
2	Polymyxin 2 mg s.c.	24	28 ± 2.0
3	Polymyxin 2 mg s.c.	17	22 ± 0.9
4	Polymyxin 2 mg s.c.	7	0
5	Polymyxin 2 mg s.c.	6	0
6	Polymyxin 2 mg s.c.	5	0
7	Polymyxin 2 mg s.c.	4	0
8	Polymyxin 2 mg s.c.	3	0
9	Polymyxin 2 mg s.c.	2	18 ± 0.6
10	Polymyxin 2 mg s.c.	1	27 ± 2.1

* The animals of all groups were conditioned with 1 mg of polymyxin s.c. on the belly and challenged immediately afterwards by 200 mg of NaCl in 2 ml of distilled water injected under the shaved skin of the back. The figures in this column refer to the time interval elapsing between pretreatment and the conjoint administration of conditioner + challenger.

ing + challenge is ineffective perhaps because the action of this mast-cell discharger is comparatively slow (especially when administered subcutaneously instead of intravenously). Here the protective effect is presumably overcompensated by the conditioning action of that portion of the first dose which reaches the circulation simultaneously with the second (conditioning) dose and hence merely adds to the conditioning effect of the latter.

Since all mast-cell dischargers tested, as well as histamine, a mast-cell product, proved to be highly potent prophylactic agents against the ACN, we had to make certain that 5-HT does not share this action. We considered this point important, because 5-HT is also a mast-cell product, at least in certain rodents (presumably including the rat), and shares with the above mentioned substances a strong conditioning action for the ACN phenomenon.

Table 6. *Absence of protection by 5-HT against 5-HT*

Group	Pretreatment	Time interval* (hours)	Necrosis (mm)
1	None	—	10 ± 6.0
2	5-HT 2 mg s.c.	24	26 ± 1.0
3	5-HT 2 mg s.c.	5	18 ± 4.9
4	5-HT 2 mg s.c.	1	32 ± 1.1

* The animals of all groups were conditioned with 1 mg of 5-HT injected s.c. on the belly and immediately thereafter challenged with 200 mg of NaCl in 2 ml of distilled water administered under the shaved skin of the back. The figures in this column refer to the time interval elapsing between pretreatment and the administration of conditioner + challenger.

The absence of protection by 5-HT could be demonstrated in the last experiment of this series in which it was tested against itself on the assumption that if it possesses any prophylactic effect, this would be strongest under these circumstances. Tab. 6 shows that no such prophylaxis could be demonstrated even when large amounts of 5-HT were administered 1, 5 or 24 hours before the conditioning + challenge. Indeed our findings strongly suggest that, under these circumstances, the effect of the pretreatment and treatment may actually be additive.

Discussion

It is evident from the data presented above that treatment with various mast-cell dischargers or such mast-cell products as 5-HT and histamine so conditions the rat that it responds to subsequent challenge (e. g., by hypertonic NaCl solution) with extensive local necrosis. The

principal result of the observations reported here was to show that pretreatment with mast-cell dischargers prevents this response.

It is tempting to assume that this type of protection is due to a precocious discharge of the mast cells which then (having lost their stores of active compounds before challenge) can no longer respond satisfactorily to a second stimulation by mast-cell dischargers given at the time of challenge. This interpretation would also be consonant with the fact that pretreatment with 5-HT (presumed to be a mast-cell product) offers no protection either against its own conditioning effect or against that of mast-cell dischargers. If the protection were dependent upon mast-cell discharge, it would be understandable that products of the mast cells (unlike their dischargers) should fail to induce it.

Another observation is also compatible with the concept that mast-cell discharge may be responsible for the protection under study here. As previously stated, the smallest dose of the mast-cell discharger, dextrin, capable of producing a full-blown ACN (when given simultaneously with the challenger), is roughly the same as the minimum dose necessary to offer protection (when administered as a pretreatment). This critical dose was found to protect almost equally well against the smallest effective and the largest tested doses of dextrin, perhaps because once the mast cells have discharged virtually all their granules, no effect can be expected even from the largest amounts of a discharger (Tab. 3).

On the other hand, histamine, another mast-cell product, did produce resistance both against itself (Tab. 1, Group 19) and against moderate doses of dextrin (Tab. 2, Group 5) or dextran (Tab. 4, Groups 16 and 17), but not against 5-HT (Tab. 1, Group 12, Tab. 2, Group 12) or excessive amounts of dextrin (Tab. 1, Group 5). While these findings do not exclude the possibility of protection through mast-cell discharge, they do suggest that other mechanisms may also be involved.

In any event, it is reasonable to assume that cyproheptadine and phenoxybenzamine act (through their well-known antihistaminic and antiserotonin activities) on the end products of mast-cell degranulation rather than on the cells themselves.

Finally, we have seen that the protection offered by mast-cell dischargers histamine, cyproheptadine or phenoxybenzamine is of comparatively short duration (Tab. 4 and 5); therein it resembles tachyphylaxis and differs essentially from the long-lasting forms of immunity offered by serologic reactions.

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